



Atty. Dkt. No. 023312-0118

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Kohichi TANAKA et al.  
Title: MOUSE DEFICIENT IN GLUTAMATE  
TRANSPORTER GLAST FUNCTION  
Appl. No.: 10/553,051  
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Date: 4/13/2004  
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Examiner: Fereydoun G. SAJJADI  
Art Unit: 1633  
Confirmation Number: 5841

**DECLARATION UNDER 37 CFR§ 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

I, Kohichi Tanaka, hereby declare:

1. I, Kohichi Tanaka, am an inventor of the above identified Application. My curriculum vitae is attached as **APPENDIX A**, including details of my experience and background.
2. I have read and understood the Office Action dated June 20, 2008, and particularly the Examiner's comments regarding the alleged obviousness for a person of ordinary skill in the art to combine the teaching of Watase et al. and Chitnis et al.
3. In response to the Examiner's above comments, I hereby provide the following information which demonstrates that it is, indeed, a surprising result that the method disclosed in this Application produces GLAST knockout mice having an intraocular pressure within a normal range ( not greater than 21 mmHg) and having at least 20% less retinal ganglions cells than a wild-type mouse.

Figure 1A

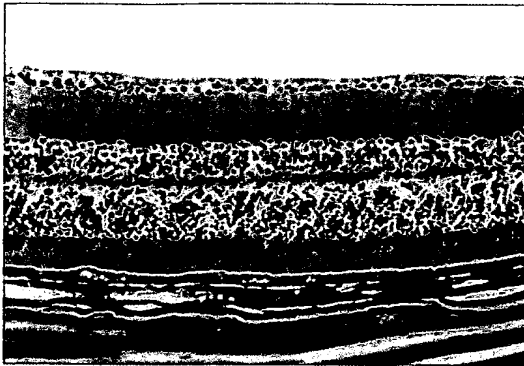


Figure 1B

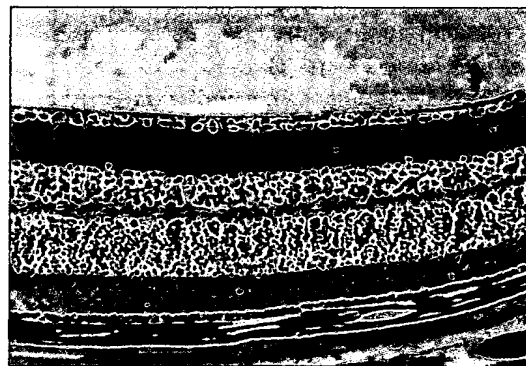
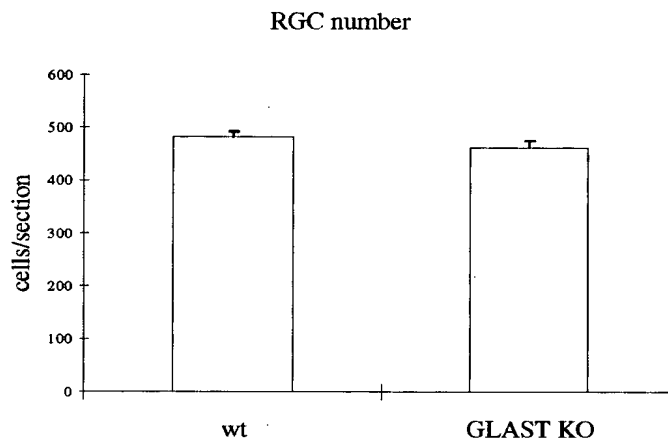


Figure 2



4. In a comparative experiment, the GLAST knockout mice were backcrossed with 129sv strains, instead of C57BL/6J strains as disclosed in the Application. The conditions of the comparative experiment are similar to that of the experiments previously described in the Specification, except that 129sv strains, instead of C57BL/6J strains, were used for backcrossing. Resulting mice were deeply anesthetized with diethylether and perfused transcardially with saline, and then treated by a 4% paraformaldehyde in 0.1 M phosphate buffer containing 0.5% picric acid at room temperature. The eyes of treated mice were removed and postfixed overnight in the same fixative and then were embedded in paraffin. Histological sections, around 7  $\mu$ m thick, were prepared along the vertical meridian, mounted, and stained with hematoxylin and eosin. Images of histological sections of a wild type mouse and of a GLAST knockout mouse resulting from backcrossing with 129sv strains for ten times are shown in Figures 1A (a wild type mouse) and 1B (a GLAST knockout mouse resulting from backcrossing with 129sv strains), respectively.

5. As shown in Figure 2, the numbers of the retinal ganglion cells (RGC) were counted from one ora serrata through the optic nerve to the other ora serrata, demonstrating that no observable reducing of the number of the retinal ganglion cells was found in a GLAST knockout mouse obtained by backcrossing with the 129sv strains, compared to that of a wild type mouse. This conclusion was confirmed by a two-tailed Student's *t*-test, resulting in a p value of 0.37. Thus, in contrast to GLAST knockout mice obtained by backcrossing with the C57BL/6J strains, significant reducing of the number of the retinal ganglion cells was not observed on GLAST knockout mice obtained by backcrossing with the 129sv strains.

6. The above experimental results show that the GLAST knockout mice backcrossed with the 129sv strains display a different phenotype from the GLAST knockout mice backcrossed with the C57BL/6J strains.

7. In conclusion, in view of the comparative experiment explained above, one of the ordinary skill in the art would not be able to predict that the GLAST knockout mouse backcrossed with the C57BL/6J strains would result in the phenotype recited in the present claims, with a reasonable expectation of success, at the time of the instant invention. Indeed, it is surprising that the step of "repeating crossing the heterozygous mouse with a normal C57BL/6 strain mouse to generate a heterozygous knockout mouse" produces an inbred GLAST knockout mouse *not only* having less genotypic and phenotypic background variation, *but also* having an intraocular pressure within a normal range (not greater than 21 mmHg) and having 20% - 50% less retinal ganglion cells than a wild-type mouse. Neither Chitnis nor any other references to my knowledge suggest such results would be possible.

9. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Kohichi Tanaka

Date: November 12, 2008

**Dr. Kohichi Tanaka**

**Kohichi Tanaka, M.D., Ph.D.**

**CURRICULUM VITAE**

**Current Appointment**

Laboratory of Molecular Neuroscience  
School of Biomedical Science & Medical Research Institute  
Tokyo Medical and Dental University

**Personal Data**

<b>Name</b>	Kohichi Tanaka
<b>Nationality</b>	Japanese Citizen
<b>Degree</b>	M.D., Ph.D.
<b>Work Address</b>	Laboratory of Molecular Neuroscience Tokyo Medical & Dental University
<b>Work Phone &amp; Fax</b>	P: 81-3-5803-5846/ F: 81-3-5803-5843
<b>Home Address</b>	2-30-8 Akane-Dai, Aoba-Ku Yokohama 227-0066
<b>Home Phone &amp; Fax</b>	P&F: 81-45-985-3186
<b>E-mail Address</b>	tanaka.aud@mri.tmd.ac.jp

**Education and Training**

<b>Degree/ Year</b>	<b>Institution</b>	<b>Field of Study</b>
M.D./ 1984	Niigata University	Medicine
Ph.D./ 1990	Graduate School of Medicine, Niigata University	Neurochemistry

**Professional/Research Experience**

<b>Date</b>	<b>Position</b>	<b>Institution</b>
1984 -1986	Assistant Professor	Dept. of Physiology, Saga Medical University
1990 -1993	Postdoctoral Fellow	Lab. of Neural Network, RIKEN under the supervision of Professor Ito M
1993 - 1998	Section Chief	Dept. of Neurodegenerative Diseases National Institute of Neuroscience
1998 -	Professor	Lab. of Molecular Neuroscience, Tokyo Medical and Dental University

**Publications**

1. Karlsson, RM., Tanaka, K., Heilig, M., Holmes, A. Loss of Glial Glutamate and Aspartate Transporter (Excitatory Amino Acid Transporter 1) Causes Locomotor Hyperactivity and Exaggerated Responses to Psychotomimetics: Rescue by Haloperidol and Metabotropic Glutamate 2/3 Agonist. *Biol Psychiatry* 64. 810-814,

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